Chapter

Algal Alginate in Biotechnology: Biosynthesis and Applications

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Abstract

Algae are recognized as the main producer of commercial alginate. Alginate produced using algae is located in the walls and intracellular regions of their cells. Its properties vary depending on the species, growing and harvesting seasons, and extraction methods. Alginate has attracted the attention of several industries, thanks to its unique properties such as its biodegradability, biocompatibility, renewability and lack of toxicity features. For example, it is considered a good encapsulation agent due to the transparent nature of the alginate matrices. Also, this biopolymer is recognized as a functional food in the food industry. It can be tolerated easily in human body and has the ability to reduce the risk of chronic diseases. Besides, it is used as an abrasive agent, antioxidant, and thickening and stabilizing agents in cosmetic and pharmaceutic industries. Generally, it is used in emulsion systems and wound dressing patches. Furthermore, this polysaccharide has the potential to be used in green nanotechnologies as a drug delivery vehicle via cell microencapsulation. Moreover, it is suitable to adopt as a coagulant due to its wide range of flocculation dose and high shear stability. In this chapter, the mentioned usage areas of algal alginate are explained in more detail.

Keywords: algae, algal alginate, immobilization, food, cosmetic, pharmaceutic, green nanotechnology, wastewater treatment

1. Introduction

Algae are photosynthetic eukaryotic organisms that are found in many environments such as sea, freshwater, and land and they are significantly important for oxygen production all around the world. Most of them are microscopic organisms, and their cell size can vary from 1 μm up to 10 m. There are around 72,500 algal species that produce different metabolites and products such as carbohydrates, proteins, vitamins, and many other secondary metabolites that have different benefits to humans and other organisms [1]. Since algae are exposed to stress in their nature, such as high UV radiation, salinity, desiccation and so on, their metabolites can have high antioxidant and anti-inflammatory activity, which make them valuable. They support almost all life forms in the biosphere, being a food source with high protein content (~20%) [2].

Alginate is an unbranched polymer which consists of two different residues; α-L-guluronic acid (G block) and β-d-mannuronic acid (M block) that are linearly

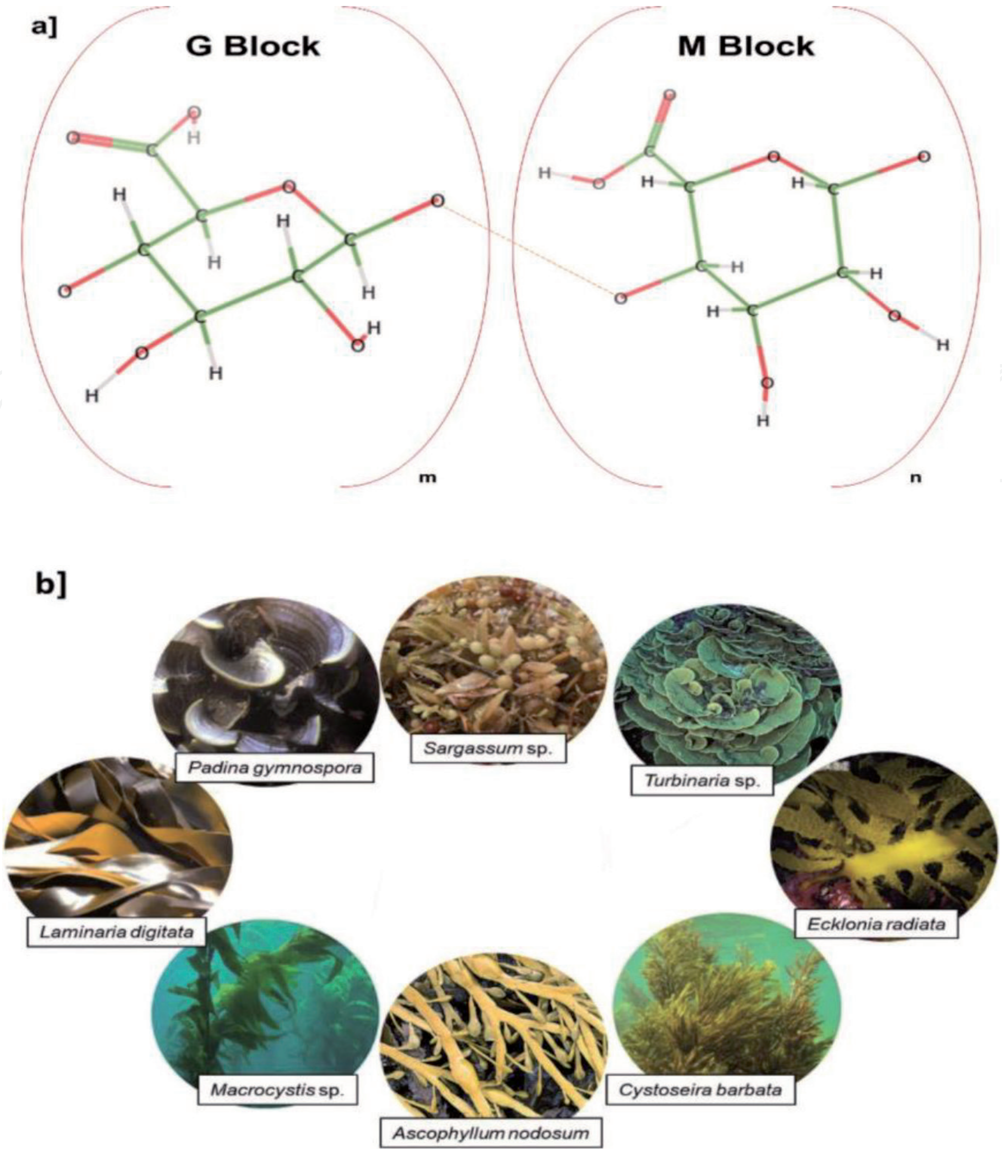

Figure 1.
(a) Chemical structure of G and M blocks; (b) Most used algae strains in alginate production [3–10].

linked together by 1–4 linkages to form the polymer as shown in **Figure 1a** [11, 12]. It is the most abundant biopolymer in the world and one of the primary carbohydrates in brown seaweeds [*Laminaria* sp., *Macrocystis* sp., *Lessonia* sp., etc. (**Figure 1b**)], reaching up to 40% of the dry weight depending on species [11–13]. A major source of alginate is the cell walls of brown seaweeds and their intracellular spaces [12]. Alginates are used commercially as thickening agents by the food and pharmaceutical industries as binders, gelling agents, and wound absorbents [11, 13]. Alginate and their derivatives and other forms such as zinc alginate, copper alginate, sodium calcium alginate, propylene glycol alginate, alginic acid, ester of alginic acid, and calcium, ammonium, and potassium salts are used in different industries in mostly textile industry with 50%, food industry follows it with 30%, and medical, cosmetic, and pharmaceutical industry with 20% of the annual production of 38,500 t alginate worldwide [12, 14].

The present book chapter focusses on alginate biosynthesis in algae and its extraction, immobilization of algae in alginate, and utilization of alginate in food and cosmetics sectors, pharmaceutical and biomedical applications, green nanotechnologies, and wastewater treatment as a coagulant.

2. Alginate biosynthesis in algae

For many years, alginate has attracted great interest in food, cosmetic, biomedical and pharmaceutical industries, and therefore the potential sources of alginate have been extensively studied to meet the commercial demand. Brown seaweeds also known as the marine macroalgae are recognized as the main producer of commercial alginate. These seaweeds (class *Phaeophyceae*) are algal species comprising complex multicellular brown algae with a wide range of sizes and morphologies [15, 16]. Their cell wall has a unique structure that contains phenolic compounds, proteins and high amount of carbohydrates. Among these components, alginate is the fundamental polysaccharide, which is found in the form of insoluble mixed salts of calcium, magnesium, sodium, barium, and potassium. There is also a large amount of alginate located in the intercellular matrix of algae and thus, total alginate content of biomass reaches up to 40% of dry weight [17]. The composition and the characteristics of alginate depend on the type of species, growth conditions, harvesting season, and extraction methods. In the work of Li et al. [18] it was shown that the chemical composition of the *Sargassum fusiforme* strain extensively varied during harvest and the highest alginate content was observed in June, whereas the alginate with maximum molecular weight and viscosity was obtained in May. In another study, a brown macroalgae *Treptacantha barbata* was cultured under four colors of light-emitting diode (LED) light including blue, red, green, and yellow and the blue LED light produced the highest sodium alginate content [19].

Today, all commercial alginates are obtained from algal sources and their composition varies among the species. The main genera containing a high amount of alginate are *Laminaria*, *Sargassum*, *Macrocystis*, *Ascophyllum*, *Lessonia*, *Ecklonia* and *Alaria* [20, 21]. Different macroalgae species and their alginate compositions are summarized in **Table 1**.

Previous metabolic studies have focused on the investigation of biological pathway of alginate synthesis in brown algae and bacteria that is another source of alginate. Despite the advances in molecular biology and genomic studies, the biosynthesis pathway and regulatory mechanism of alginate in algae have been poorly characterized. However, several studies of bacterial and algal alginate production have shown striking similarities in the basic pathway and thus these findings may provide strong clues regarding the mechanism in seaweeds [35, 36]. The molecular bases of alginate production begin with the fructose-6-phosphate and it is converted to guanosine di-phosphate-mannuronic acid (GDP-ManA) with a series of enzymatic transformations. Various enzymes including, mannose-6-phosphate isomerase (MPI), phosphomannomutase (PMM), mannose-1-phosphate guanylyltransferase (MPG), GDP-mannose/UDP glucose-6-dehydrogenase (GMD/UGD) are responsible for the synthesis of alginate precursor [35, 37]. GDP-ManA is then transferred across the cytoplasmic membrane and polymerized to the polymannuronate by the membrane-anchored proteins. After this stage, it may contain some residues unrelated to the alginate structure and it undergoes a modification step consisting of epimerization and degradation. The epimerization process is carried out by the mannuranoate C5-epimerases (MC5E) conducting the isomerization from mannuronic acid to guluronic acid. It should be underlined that the alginate synthesis route in bacteria differs from algae with the O-acetylation process that protects the produced alginate from degradation [38]. Finally, alginate polymer, composed of α-l-guluronic acid and the β-d-mannuronic acid, is formed, exported through the outer membrane, and released from the cell. Evidence for the biosynthesis of this polysaccharide within brown macroalgae come from a few studies with a limited number of species

Macroalgae species	Alginate yield (%)	References
Sargassum filipendula	17.2 ± 0.3	[22]
Sargassum vulgare	40	[23]
Sargassum wightii	33.18 ± 0.22	[21]
Sargassum angustifolium	3.5	[24]
Sargassum fluitans	9.36 ± 2.51	[25]
Sargassum muticum	13.57 ± 0.13	[26]
Sargassum natans	23 ± 1.6	[20]
Padina gymnospora	16 ± 0.7	
Padina antillarum	22 ± 1.1	
Laminaria digitata	29 ± 4.2	
Macrocystis pyrifera	26 ± 0.6	
Sargassum sp	31	[27]
Turbinaria sp	30	
Hormophysa sp	31	
Fucus spiralis	25 ± 0.21	[28]
Bifurcaria bifurcate	24 ± 0.12	
Ecklonia radiata	44 ± 0.15	[29]
Nizimuddinia zanardini	24 ± 0.8	[30]
Cystoseira barbata	9.9 ± 0.8	[31]
Padina pavonica	28.7	[32]
Ascophyllum nodosum	23.13	[33]
Durvillaea potatorum	55.2 ± 0.51	[34]
Seirococcus axillaris	41.3 ± 0.66	

Table 1.
The alginate content of various algae species.

such as *Ectocarpus siliculosus*, *Saccharina japonica* and *Laminaria digitate* [35, 37, 38]. Therefore, further research is needed to understand the metabolic route of alginate synthesis and to control the mechanism in different algae strains.

3. Extraction of alginate from algal material

Commercial alginate is mainly obtained from the biomass of brown macroalgae, and the conventional extraction process consists of multiple steps integrated to maximize product yield. Generally, the protocol begins with a pretreatment stage in which harvested and dried biomass is exposed to an acidic solution in order to break the cell wall, solubilize the relevant components, and reduce the viscosity of alginate to a desired level [26]. The second step is the alkali extraction, which is the most critical part of whole process because it greatly affects the yield and specific features of extracted alginate. At this stage, acidified biomass is treated with a strong alkali solution mostly sodium carbonate or sodium hydroxide in order to recover the alginic acid as soluble sodium alginate. The residue is removed with centrifugation or filtration and then the obtained extract is precipitated with the use of calcium chloride, hydrochloric acid, or sulfuric acid so as to precipitate alginates

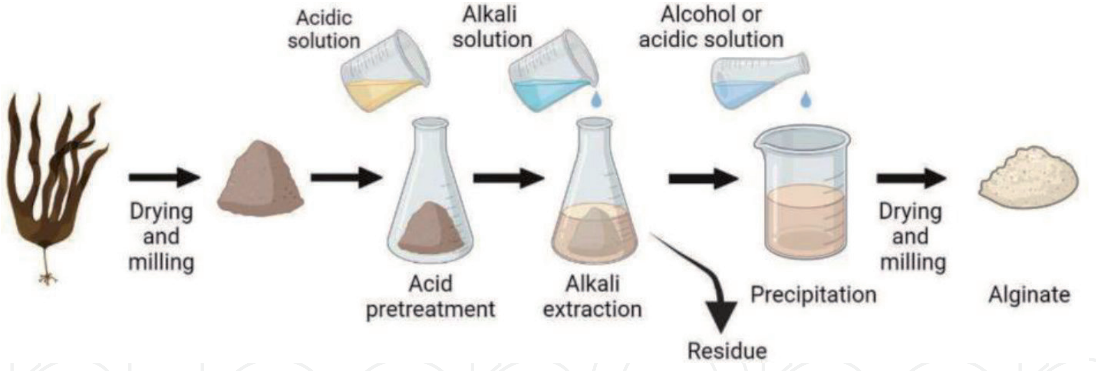

Figure 2.
Classical alginate extraction procedure from macroalgae.

in their acid or calcium salt form. Finally, the alginate product is dried, milled and ready for commercial use (**Figure 2**) [17, 39].

At the industrial level, the classical extraction method of alginate is widely used but it is highly complicated, time-consuming and requires high amount of solvents and chemicals. Therefore, novel approaches are suggested from several studies for the development of more suitable and effective extraction process (**Figure 3**). Sugiono et al. [40] performed an extrusion-assisted extraction procedure and optimized the key parameters (brown algae: solution ratio, feed rate and pH) for the alginate extraction from *Sargassum cristaefolium*. They reported that the extraction yield at optimum conditions reached the value of 34.96 ± 0.09%, and twin screw extruder was a promising method to extract alginate at the industrial scale. Youssouf et al. [41] proposed ultrasound-assisted extraction of alginate from *Sargassum muticum* to maximize extraction yield, minimize the use of chemicals, and shorten the process time. In another study, the deep eutectic solvent method combined with the subcritical water extraction technology were performed for the production of alginate from seaweed *Saccharina japonica*. The optimal conditions of different parameters were 150°C, 19.85 bar, 70% water content and 36.81 mL/g

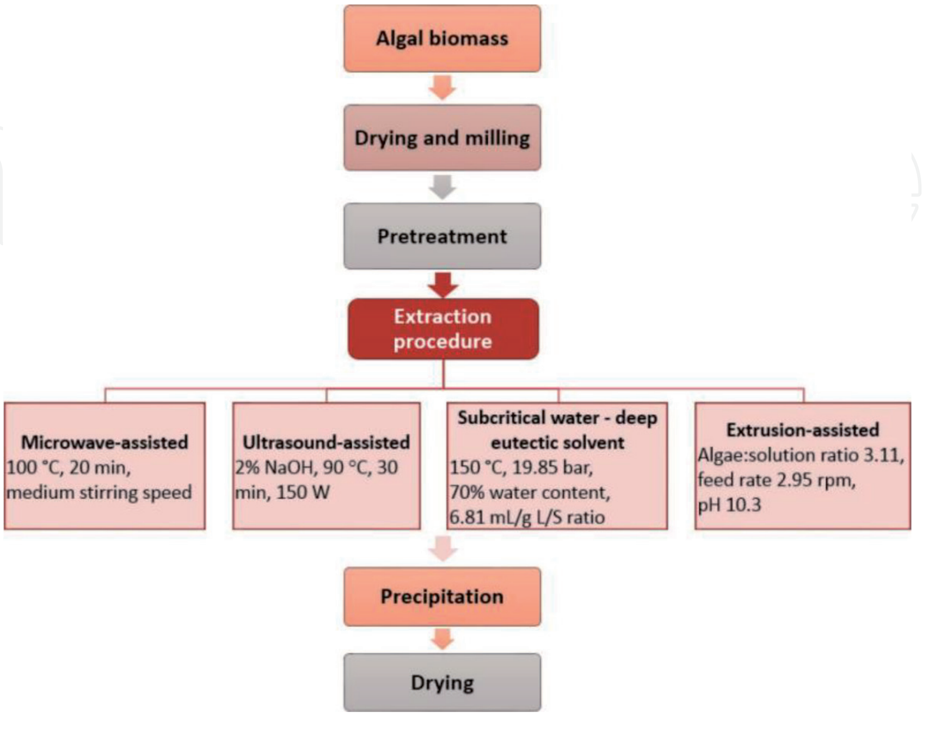

Figure 3.
Flow diagram of different extraction techniques from literature [40–43].

liquid/solid ratio giving an alginate yield of 28.1%. Also, the subcritical extraction method was defined as a clean, time-saving and effective process for the alginate extraction from seaweeds [42].

More recently, there has been a growing interest in the application of green technologies and biorefinery approach for the extraction of biological compounds. In this context, the development and optimization of biorefinery processes that integrate a sequential extraction steps in order to release multiple products of brown macroalgae is considered an effective, timesaving and green procedure. Several authors examined the extraction of a couple of components including alginate, fucoidan, laminarin, sugar, and so on with a biorefinery concept [33, 44, 45]. Yuan and Macquarrie [33] developed a step-by-step process to obtain a variety of products from *Ascophyllum nodosum* seaweed by the assistance of microwave technology. These products include fucoidan, alginates, sugars, and biochar (algae residue) and the obtained yields were 14.09, 18.24, 10.87, and 21.44% respectively. Kostas et al. [44] designed a bio-refinery procedure using *Laminaria digitata*, based on the extraction of the alginate and fucoidan, the subsequent production of bioethanol, and also the identification of bioactive compounds remaining in the residue. After the extraction of polysaccharides with the use of the conventional treatment method, the compositional structure of residue was analyzed and a high amount of glucose was determined, making this residue a potential feedstock for bioethanol production. This residue was exposed to acidic hydrothermal pretreatment and enzymatic saccharafication to release utilizable glucose and then it was fermented using *Saccharomyces cerevisiae* achieved an ethanol yield of 94.4%. Abraham et al. [45] developed and optimized a biorefinery process to extract polysaccharides of laminarin, fucoidan, and alginate from *Durvillaea potatorum*. The results established a novel biorefinery process for the extraction of multiple seaweed polysaccharides that could be used in specific industrial applications.

4. Immobilization of algae in alginate

Microalgae are one of the most remarkable species utilized in biotechnology for numerous purposes. They are crucial for biofuel production [46], bioremediation, and biotransformation [47], fuel cells applications [48], and also for wastewater treatment [49]. For this matter, the adaptation of efficient immobilization methods for microalgal applications is crucial to develop novel manufacturing strategies (**Table 2**). Most of these industries require low-cost and easy immobilization methods, of which alginate is one of the most profound encapsulation agents can serve this demand [63]. Additionally, due to their transparent nature, alginate matrices do not interfere with the photosynthetic efficiency of algae [64]. Various microalgae (*Chlamydomonas reinhardtii*, *Chlorella sp.*, *Botryococcus braunii*, *Tetraselmis sp.*, *Nannochloropsis sp.* and *Scenedesmus sp*.) and cyanobacteria (*Anabaena sp., Nostoc*, *Spirulina*, *Oscillatoria sp.*, etc.) species have been explored in immobilized matrix systems as beads, biofilms, and various geometries [61, 64, 65].

Biohydrogen as a green alternative fuel is known to be produced by microalgae species under anaerobic conditions [66]. Although microalgae are important for biohydrogen production, large-scale operations are hindered due to the oxygen sensitivity of hydrogenase enzymes [67]. Successful immobilization of *Chlamydomonas reinhardtti* and several other cyanobacteria species are promising to increase the biohydrogen production capacity of immobilized microalgae as densely packed biohydrogen micro factories [61, 62].

Microalgae in wastewater systems can also be immobilized with alginate for the continuous removal of nitrogen and phosphorous to decrease organic loads of

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Target	**Aim**	**Advantage**	**Disadvantage**	**Mode/Approach**	**Common microalgae species**	**References**
Wastewater treatment/ Bioremediation	Removal of wastes and polluting chemicals	Reduced cost at downstream operations Enhanced cell survival Durable and long-term cultivation Continuous removal of nutrients, heavy metals, suspended solids and toxic organic compounds	Slower removal of phosphorus	Packed bed Airlift photobioreactors Biofilm photobioreactors Immobilized sheets Suspended alginate beads	*Scenedesmus dimorphus* *Chlorella vulgaris* *Spirulina platensis* *Chlorella sorokiniana* *Dunaliella salina*	[50–53]
Biotransformation	Decrease the toxic effect of compounds in aquatic systems Endocrine disrupting components Polycyclic aromatic hydrocarbons Phenolic compounds Dyes	Low capital cost High removal rates Small scale operations	Limited knowledge on microalgal biotransformation metabolism Requirement of extremophilic algae species Toxicity of the compounds to the algal cells	Suspended beads Immobilized alginate sheets Packed bed columns Airlift photobioreactors Biofilm photobioreactors Immobilized sheets	*Chlorella vulgaris* *Phormidium sp.* *Prototheca zopfii*	[54–57]
Biosensor	Environmental monitoring for aquatic and soil quality as toxicity bio-indication Suitable for agricultural and aquaculture purposes	Real time analysis Rapid pollutant removal	Disruption of alginate networks in water Dehydration and decomposition of the biosensor Lower detection quality	Disruption of PSII electron transfer by herbicides and other toxic molecules	*Chlorella vulgaris* *Chlamydomonas reinhardtii*	[58, 59]
Culture collection and handling	Increasing the success of long-term microalgae storage	Sustained metabolic activity at 4°C Time and cost efficient	Lack of standardized methods as it is in animal cell cultures	Immobilization in alginate beads or surfaces	Various important biotechnological species	[60]
Biohydrogen	Increasing the biohydrogen production efficiency and productivity	Prolonged hydrogen production compared to suspension cultures Enhanced cell viability in anaerobic cultures Decreased sensitivity to oxygen	Scale up Degradation of alginate in aqueous environment	Beads Sheets Tubular bioreactor Bubble column photobioreactor	*Chlamydomonas reinhardtii* *Anabaena sp.* *Synecocystis sp.* *Tetraspora sp.*	[61, 62]

Table 2.
Microalgae immobilization methods.

wastewater systems [53–55]. This approach is a clean and sustainable understanding for wastewater treatment, which inspired the utilization of microalgae for bioremediation purposes [68, 69] and removal of heavy metals [50] and other toxic molecules in the aquatic systems. There are also novel concepts to use immobilized microalgae networks as biosensors to check soil and water quality [58, 59].

Co-immobilization of different cell types can enhance the immobilized microalgae consortium. Microalgae growth-enhancing organisms can enhance the biomass accumulation in immobilized systems, which can increase the efficiency of immobilization for wastewater treatment, bioremediation, and biotransformation purposes [70, 71]. Symbiotic systems of algae-fungi in matrices can increase the efficacy of immobilization and decrease the toxic harms of heavy metals on algae [72].

Although alginate can provide a good environment for microalgae, there are several limitations concerning the stability of alginate gels. In aqueous systems, due to the diffusion of Ca^{+2} ions to aqueous environment, the alginate network can loosen, which subsequently damage the network. Thus, designer gels and/or blends with several other hydrogels can increase the durability and mechanical properties of alginate network [63, 73]. Another important aspect is although alginate does not affect cell proliferation, denser cultures may be needed, or due to dense culture diffusion limitation may increase cell death [62].

5. Algal alginate in food sector

Recently, food consumers have begun to consider nutrition contents of foods and desire more natural foods instead of the synthetic ones. As a result of that, foods which contain alginate as a natural substance have become more popular [74]. Most importantly, the United State Food and Drug Administration (U.S. FDA) has classified the alginate as "generally regarded as safe" and European Food Safety Authority (EFSA) has recognized to use it in specific doses [75, 76]. In the food sector, alginate has many uses as food production, packaging, thickening and, stabilizing agents, thanks to its unique properties like biodegradability, biocompatibility, renewability, and lack of toxicity [17, 74, 75, 77–79]. It has been noticed that alginate is easily tolerated in human body [80]. For this reason, it has been harmlessly inserted in a wide range of food products. Those can be listed as tinned, baked and, frozen foods, meat, poultry, salad, seafood, pet food, cheese, fruit, beverage, jelly, dessert, jam, ice cream, sorbet, and mayonnaise [17, 76, 81–84]. Additionally, it is considered functional food that has ability to reduce the risk of chronic diseases and make them more controllable [17, 85]. Thus, it enhances the quality of life due to its anticancer and probiotic features [17]. In addition, it can be applied to dairy liquid products, beer, and drinks which are consumed by diabetic patients [17, 80]. Also, adding alginate in the foods decreases the transit time in the colon and this situation helps human body to prevent from colon cancer [86, 87]. Moreover, as a result of having the ability to reduce the feeling of hunger, this polymer can be consumed to cure obesity [17, 86]. Moreover, it induces gastrointestinal disorders and the risk of coronary heart diseases [15, 87, 88]. Alginate is used in food products in the range of 0.5–1.5% [87]. For example, Na-alginate can be used without any unhealthful side effects at the highest dose of 15.5 mg Na-alginate/kg $(day)^{-1}$ [15]. Zn concentration should be carefully considered when Zn-alginate combination is used in food products. Because a high concentration of Zn^{2+} has negative effects on human body like nausea, diarrhea, and other diseases in the digestive system. So, its concentration must be in a suitable range. Zn-alginate can be added to purple corn to prevent the color in the drinks. Ca-alginate can be applied in yogurt, jams, and salads to control their smooth taste, in ice-cream to balance the crystal statement, and in noodles to increase the cohesion [78]. Propylene glycol-alginate can be included in salads and sauces [83]. Al^{3+} exhibit higher stable Al-alginate mixture than Ca^{2+} and Ba^{2+}, thanks to its three-dimensional binding model. But it is possibly toxic and is not safe for using in food products. Unfortunately, Al-alginate uses in food industry are limited as packaging material of conserve meals [78].

The food package is used for covering the product for protection, preservation, containment, and conservation purposes. After the food product is produced, physical/mechanical damages, physicochemical, and biological changes can occur. As a result, the quality and safety of the food may be decreased. In order to avoid this, synthetic compounds have begun to be used as a packaging material. Thereafter, it has been noticed that synthetic package materials are liable for a huge amount of waste that is detrimental to marine and wildlife. Therefore, researchers have been focused on finding new natural compounds that can be a promising candidate as a food packaging material [76]. After many experiments, they have been established that alginate has the ability to decrease lipid oxidation, microbial contaminations, nutrition lost, and wizening. Thus, this polymer improves the foods shelf life and keeps them fresh [76, 78, 89]. Nowadays, alginate is used for packaging in a wide range of food products like potato strips, pineapple, sweet cherry, peach, melon, pork, and beef balls, roast beef, chicken meat, chicken nugget, chicken ball, hams, salmon, bream, perch, mozzarella cheese, coffee, powdered milk, resoluble tea, fresh cut foods like apple, carrot, and mango [15, 76].

Nowadays, 3D food printing is an efficient technology to produce high valuable food products. While printing the food, encapsulation of significant compounds (antioxidants, vitamins, probiotics, etc.) with alginate increases the strength of foods against the negative effects of light, heat, and oxygen at preparation and storage stages. The most important problem in this regard is the tendency of food products to deteriorate geometrically. At this point, the alginate improves the water dispersion and thus provides more stable products with good mechanical and thermal behavior [74].

Alginate can be utilized as a good thickening agent, thanks to its adhesion and cohesion features. Pure alginate shows a high viscosity ten times more when compared to commercial thickeners. Also, it has the ability to enhance food properties like its texture, organoleptic situation, and consumer acceptance. For example, it can improve yogurt's shape, creamy texture, adhesion feature and restrain the viscosity at the sterilization step. Also, this polymer can be added to the jelly to decrease the difficulty involved in swallowing [78].

In food applications, there are many molecular surfactants that are used as a stabilizer; they have negative effects on human health and environment. As a result of this, researchers have been focused to find new solid particles that can be used instead of molecular surfactants. Solid particles are divided into two groups as inorganic and naturally derived. Unfortunately, inorganic particles have a limited area of usage [77]. Because of that, a rapid increase in the tendency to use surfactant derived from natural sources was observed [77, 90]. In this case, alginate can be added to the beer for stabilizing the foam as a stabilizing agent [78, 83]. Additionally, alginate can be mixed with oil droplets for the preparation of emulsion gels, which are used in mayonnaise and similar foods [78].

Alginate has the ability to combine with two different cations to form a gel. Alginate contained products have significant elasticity that is controllable by changing the ratios of ions and alginate concentrations [78, 91]. Besides having this unique property, algal alginate may include some impurities like heavy metals, polyphenols, proteins and endotoxins because it is a natural compound [17, 79]. In the food industry, low levels these impurities can be acceptable, but in the cosmetic industry, they have to be removed [79].

6. Algal alginate in the cosmetic industry

A cosmetic product can be defined as any natural or prepared material that in contact with teeth and mucous membranes of the mouth cavity and external parts of human body (epidermis, hair, nails, lips, and external genitals). These products can be in different forms as cream, lotion and spray. Nowadays, many people use cosmetic products and their ingredients, some for therapeutic purposes and others to enhance their beauty [92]. However, it should be noted that the purpose of using a cosmetic product cannot be to cure any parts of the human body. This kind of products are generally used after different dermatological issues like acne, eczema, and so on [93]. Recently, a new word called "cosmeceutical" has been used to indicate specific cosmetic products, which include active ingredients. These products are not considered drugs or cosmetics, but they show medical or drug-like benefits. The cosmetic/cosmeceutical consumers desire the products that are safe, effective, protective, elastic, and natural with good quality [91, 92].

Recently, cosmetic consumers have begun to pay attention not only to the effects of the product as a whole, but also to the content of the products [94]. With the increase in acquiring knowledge about the ingredients, awareness about the unhealthful side effects of synthetic cosmetic ingredients (irritation, allergic reactions, etc.) is created among the consumers more than before [91, 93, 94]. Additionally, Cosmetics Europe – the community for the cosmetics and personal care industry – has forbidden the use of synthetic solid plastic particles, which cannot be biodegradable by marine organisms for saving aquatic ecosystem in any types of cosmetic products [95]. This situation has contributed to conduct more research on finding new, natural, eco-friendly and biodegradable polymer sources to produce natural ingredients [91, 95]. At this point, algal alginate has drawn attention, thanks to its biological activities as an anticoagulant, antiviral, anticancer, antimicrobial, moisture retention, anti-irritating, antioxidant, anti-inflammatory, and antibacterial matter [17, 78, 90, 91]. As a result of having these aforementioned properties, alginate can be used as an abrasive agent, antioxidant, and thickening and stabilizing agents in the cosmetic industry [17, 90]. From this point of view, algal alginate is a promising candidate as a cosmetic ingredient.

The skin is the biggest organ of the human body and covers all the other organs [74, 91, 96]. It has three layers: epidermis, dermis, and hypodermis. The epidermis is composed of five stratums: basal, spinous, granular, lucid, and corneum. This layer contains melanocytes, langerhans, keratinocytes, granules, and dead keratinocytes [91, 93]. Melanocytes include melanin that determines the skin color and both of the melanocyte, and keratinocyte cells heal the skin damages. The stratum corneum acts like a water diffusion barrier. Thus, it protects the skin from dehydration and irritation and allows the human to live in air [91]. The health situation of the cells on the epidermis layer changes according to the weather conditions and nourishment schedules. Dead cells remain on the skin nearly for two weeks. After that, they through desquamation and recuperation stages and these stages take one month. Peeling products have the ability to remove dead cells and improve skin health without causing any negative effects on the skin. In this way, these products can help to make these processes faster [93]. Researchers have found that the optimum diameter of microparticles which is used in the peeling product formulation is 750 μm. Alginate microparticles are a good candidate as abrasive agents, thanks to their regular and spherical shape. The addition of starch to these microparticles increases the surface unevenness and inequality. This starch-alginate microparticles combination shows the effect on the skin as synthetic balls do. They have a unique potential for replacement with synthetic ones, as they are natural, biodegradable and environmentally friendly compounds [95].

Naturally the skin has the ability to synthesize antioxidant agents to protect itself from reactive oxygen species (ROS). Also, it has been known that the skin increases ROS production when exposed to UV radiation. Under these circumstances, oxidative stress causes the existence of wrinkles, dehydration, inflammation, melanoma, and skin cancer. For preventing skin aging and other aforementioned cutaneous disorders, the skin has to be supplied by antioxidants via cosmetic products [91, 93]. At this point, algal alginate is a promising candidate as a cosmetic ingredient with significant antioxidant activity [80, 91]. This activity related to its molecular weight, sulfate content and anionic groups [97]. Thus, it can be used as anti-aging, anti-wrinkle, and smoothing agents [93, 98]. Additionally, it has the ability to absorb several 100 times more water than its own weight to support the cell and regulate the water distribution in the skin, and thus protect cells from caving in [15, 91, 98]. Considering these properties, it has been inserted in a wide range of products such as hand lotions, ointments, fat-free creams, facial masks, and dental materials to improve nutrients diffusion and absorption [78, 80, 99].

Alginate can be used as thickening agent in shampoos, lotions, or other cosmetic products, which include huge amount of water for instability inhibition purpose [98]. Also, this polymer has ability to stabilize the viscosity to offer good liquidity in cosmetics [79]. This is the major reason of using it in cosmetic formulations [91]. Also, it helps to maintain the organoleptic features (taste, sight, smell, and touch) of cosmetics, thanks to its favorable activities [80, 91].

7. Algal alginate in pharmaceutical and biomedical applications

Although the biocompatibility of alginate has a debate, it is still one of the mostly studied polymeric biomaterials in pharmaceutical and biomedical applications for tissue engineering and regenerative medicine (TERM) purposes [100]. Alginate can be fabricated in various shapes and forms (**Figure 4**) for an extensively wide application (**Figure 5**). Alginate provides a biocompatible, cost-effective, low toxicity, and also easy gelation. Currently due to high viscosity and rheological properties with respect to increasing concentration, alginate is utilized as stabilizer and thickeners in pharmaceutical formulations. However, due to increased utilization of hydrogels in TERM, alginate-based formulations are extensively investigated as controlled drug-release platforms and tissue-engineering constructs [104–106].

Kinetic release of pharmaceutical compounds such as drug molecules, proteins, peptides, and nucleic acids is a novel advanced therapeutic approach [107]. Although alginate is a polar biopolymer, amphiphilic design of the alginate, or blending with other polymers can alter the hydrophilicity, thereby enabling the release of hypophobic/amphibic molecules [73, 103]. Alginate also creates a mild environment for proteins and other molecules, which can be affected by heat or alkali conditions resulting due to denaturation. Also, enzymes can be encapsulated with algae to have a controlled biocatalytic conversion. Alginate is usually ionically cross-linked with bivalent cations which is a low-cost and rapid method of gelation. However, when alginate is in an aqueous environment, bivalent cations are released into the environment, which makes a faster release of entrapped drug molecules based on their hydrophilicity, size, and interaction with alginate. In order to increase the control over the alginate, chemical modifications are done to chemically functionalize alginate for thermo-responsive, pH-responsive, or light-responsive matrices [108].

Wound healing is a complex phenomenon starting from inflammation, cell migration to the wound site, and eventually remodeling of the wound healing area [109]. Recently hydrogel-based wound dressings are gaining attention, and alginate

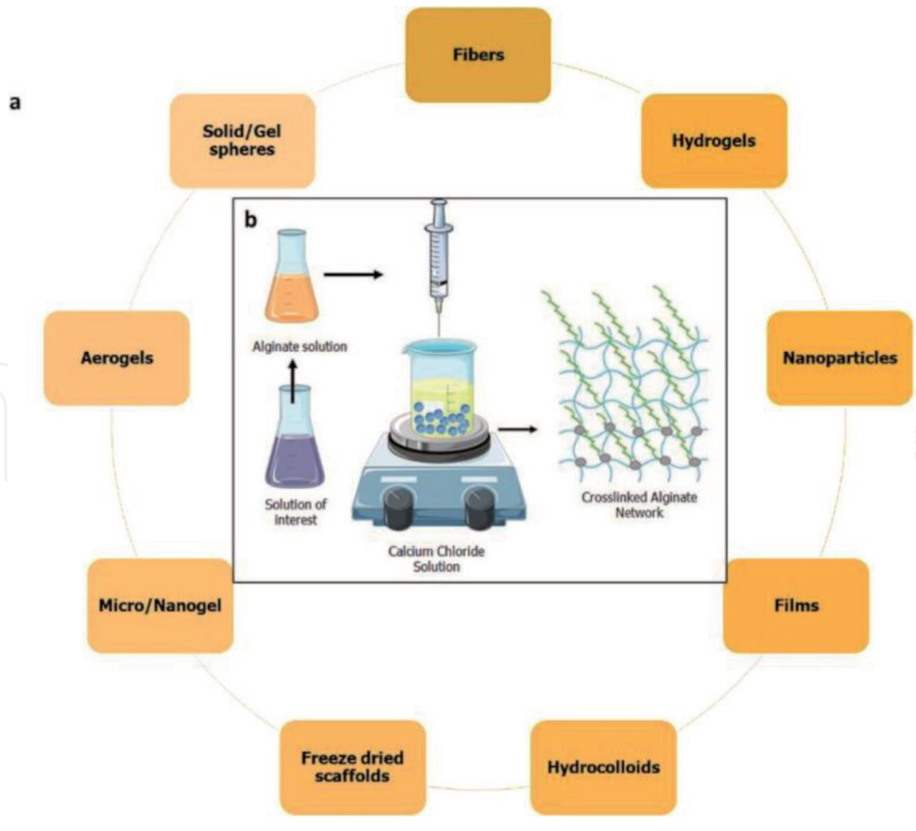

Figure 4.
Alginate in shape (a) fabrication forms of alginate for various application [61, 62, 100–102]; (b) classical immobilization method for alginate crosslinking.

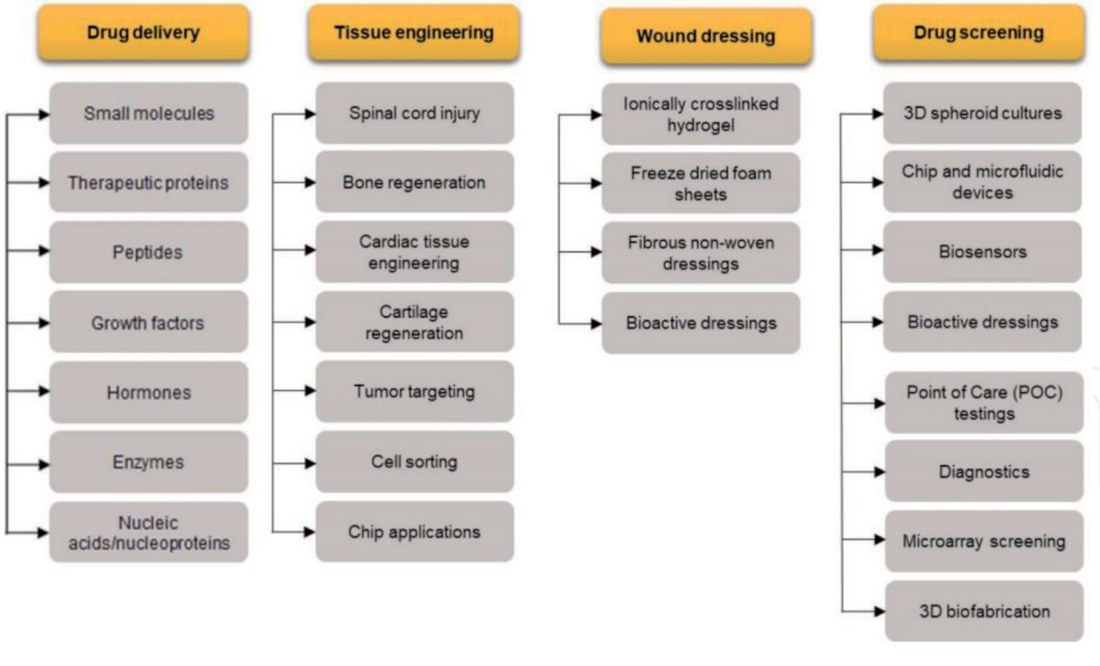

Figure 5.
Application areas of alginate in pharmaceutical and biomedical purposes [64, 100, 102, 103].

is one of the most studied and also commercially available wound dressing patches [103, 107]. Due to high water content and immobilization of bioactive molecules inside the patches to create antibacterial, anti-inflammatory and growth factors to promote cell growth and healing alginate are considered a gold standard in these types of applications.

3D cell culture is gaining interest because 2D cell culture does not correspond to the signals of cells in their nature. 3D environment creates a biomimetic environment to understand cell behavior, drug response, and 3D tissue culture [64, 102, 110]. Alginate creates a good environment resembling the extracellular matrix (ECM) structure where cells can proliferate and differentiate. Also, alginate can be covalently linked to cellular attachment sequences (mostly utilized RGD) to increase cell-cell interactions and cell-surface interactions [101, 111]. Encapsulation of growth factors in these 3D gels can increase the cell differentiation [104], neotissue formation, and blood vessel development [102, 112].

Alginate can also be a base hydrogel for 3D biofabrication purposes [111, 113]. Due to the availability of advanced imaging methods, these constructs can be customized as a personalized medicine tool [114]. However, due to the low mechanical properties of alginate, the bioprinting is usually done with blends with other hydrogels such as collagen [112], gelatin [111], chitosan [115] or self-assembling peptide hydrogels [104, 106].

Although alginate is a biocompatible and a plant-based biomaterial, the biodegradation of alginate can be troublesome. Alginate does not degrade in the body; however, due to the release of ions form the network, it decomposes into small pieces. Thus, chemical modification such as oxidation of alginate chains may help to achieve a proper biodegradation for clinical applications [116]. Moreover, low mechanical properties and stiffness may hinder the utilization of alginate, especially for hard tissue engineering. Chemical modification may elevate the material properties. However, it may add toxicity to the compound too. Nevertheless, as in vitro drug testing [117] and 3D cell culture platforms [111], even for topical applications [103], alginate is a safe natural biomaterial. It is also highly promising for tissue engineering applications, especially as injectable formulations [104].

8. Algal alginate in green nanotechnologies

Nanotechnology aims to have structures that have a size in a nanometer scale (less than 100 nm) to be produced and applied to provide purposeful design. Nanomaterials, which are a product of nanotechnology, have exceptional surface activity and other physical properties that occur due to their shapes at nanoscale sizes. In the last decade, nanotechnology has gained popularity and it has been used in different fields such as medicine, pharmaceuticals, cosmetics, food, and clothing industries. Production of synthetic nanomaterials is expensive and not an environmentally friendly process, even though they have many applications and benefits today. It is not safe to use them in medicinal applications due to their risks and side effects and the difficulty to form gels in situ. Hence, green routes to synthesize nanomaterials, which is called green nanotechnology has gained attention. The aim of green nanotechnology is to reduce the risks and to solve environmental problems related to nanotechnology [118, 119].

Natural polymers such as alginate, chitosan, agarose, collagen, cellulose, and so on have been used as nanoparticles (NPs) due to the concerns about synthetic ones [118]. Characteristics of these NPs such as small surface area to volume ratio, structural surfaces, agglomeration, and enhanced reactivity make them to be applied in various areas such as cancer therapy, drug targeting, nano-pharmacology, nanomedicine, and agrochemical delivery [120]. In recent times, the most widely used polymer is alginate, since it is considered safe especially for human applications. Alginate is considered to be safe owing to the fact that it has been studied extensively, even though other biomaterials can be good alternatives in the future, However, alginate has properties that offer advantages to the system and make it a perfect fit for biotechnology and drug delivery systems via cell microencapsulation [118]. Temperature and pH changes, signaling molecules, and enzymes stimulate a drastic chemical and physical change in alginate, which results in making them a potential candidate for drug delivery vehicles [121]. Biocompatible and nontoxic polyionic complex NPs are formed through ionic gelation of alginate and chitosan. These polyionic complexes are used in drug delivery and wound healing purposes because they are non-toxic and biocompatible as well as have effective protection of biomolecules [122]. Natural nano carrier systems can be easily integrated with antiviral, antifungal, antituberculosis drugs, and so on. For antituberculosis drugs, lipid-based formulations and polymer-based formulations are used. Lipid-based formulations have drawbacks with successful targeting, since it is dependent on the parenteral/inhalable route, whereas alginate is already FDA approved for human use and it is successful with the oral treatment of reflux esophagitis as well as being a popular pharmaceutical excipient. Hence, alginate-based carriers have gained popularity in drug targeting. The recent studies prove that if alginate NPs are used, the outcome could be further improved in the sense of encapsulation of drug, pharmacokinetics, bioavailability, and therapeutic efficacy [123]. Alginate NPs can also be used as a carrier for adjuvants and vaccine immunogenicity is increased, since alginate nanocarriers can prolong the release. Agglomeration has not occurred in major organs through the use of alginate NPs. Mucoadhesive properties enhance the permeability of alginate NPs and therefore it is being used in nasal and oral administrations; degradation is reduced in acidic environment [124].

NPs of alginate can be used in agriculture as a nanopesticide, nanoinsecticide, nanoherbicide, nanofertilizer, growth stimulants, pesticide carriers, antimicrobial agents, and nanoformulations [125]. Targeting and systemic delivery of herbicides can be provided by using nanocapsules with alginate/chitosan NPs [126]. Chitosan and alginate as carriers of herbicide and insecticide do not only improve the release of the herbicide but also improves its interaction with the soil [126, 127]. Chitosan/alginate NPs can also be used as nano carriers for pesticides, herbicides, and fungicides. Slow release of the molecule can be provided and NPs can protect them from UV radiation and it offers a better antifungal activity [120].

9. Algal alginate as a coagulant in wastewater treatment

Coagulation is a process used in water treatment, in which aids are used to change the surface structure of suspended materials to form aggregates and to remove them by destabilization. In this process, inorganic metals and polymers are generally used as coagulation aids [128–130]. The large amount of chemicals, significant pH changes, and the high amount of sludge produced are among the significant disadvantages of the coagulation process with metal salts [128, 129]. In addition, some negative effects of synthetic polymer on human health have increased the tendency to use natural polymeric materials as a coagulation agents. Natural polymeric materials such as polysaccharides are low cost, easy to obtain, have low molecular weight and high shear stability. For these reasons, they have been suggested to be more advantageous materials. They also have advantages such as being safe for human health, biodegradable, and having a wider effective flocculation dose range for various colloidal suspensions [129, 131]. High volume wastewater is one of the most important problems for many industrial sectors. Especially, textile industries produce large volumes of wastewater with varying physicochemical properties. This diversity in physicochemical properties is due to the enormous continuous effort to identify suitable technologies for the treatment of textile industry wastewater and the many components involved in this process [130, 132]. The different types of wastewater treatment performed for industrial wastewater include coagulation/flocculation, oxidation, membrane separation,

ion exchange, photochemical, adsorption, biological treatment method, and so on [130, 133]. Among the various methods, one of the effective methods for removing substances from wastewater is coagulation using algal alginate [130].

Alginate naturally derived from algae offers significant potential for wastewater treatment as a coagulant. Calcium and sodium ions can be used as coagulation aids in processes where alginate is used as a coagulant. Especially when calcium ions interact with metal cations in the alginate structure, the gel structure forms and tends to precipitate the pollution factors in the wastewater. Thanks to having the ability of formation insoluble molecules, it becomes an important option as a coagulant in wastewater treatment [130, 134–136].

Laboratory-scale studies on the use of the obtained algal alginate in wastewater treatment processes have been carried out. In these studies, the process continues with measuring the coagulation efficiency depending on the determined parameters after the extraction stage. In the study conducted by Vijayaraghayan and Shanthakumar [130], *Sargassum sp.* was used as an alginate source and the efficiency of removing Congo red dye from the aqueous solution was studied depending on the pH, alginate dose, calcium dose, and initial dye concentration of the extracted alginate. As a result of the study, it has been shown that the performance of alginate as a coagulant is highly dependent on the calcium dose used as the gelling agent and the initial dye concentration in the solution [130]. A process for reactive magenta dye removal in textile wastewater was carried out depending on the alginate dose, calcium dose, and pH by the same authors. In this study, a color removal of 92.7% was achieved and it was confirmed that the alginate extracted from *Sargassum sp.* could be used as a coagulant for dye removal in textile wastewater [137]. In another study conducted by Natesh et al., 3 different algae such as *Sargassum* sp., *Turbinaria* sp., and *Kaapaphycous alvarezii* were used and the results supported the study obtained by Vijayaraghayan and Shanthakumar [129]. In the study by Devrimci et al., the coagulation efficiency of algal alginate was investigated in terms of drinking water treatment. The study was carried out depending on parameters such as calcium and alginate doses, and the initial turbidity of the samples. Experiments on synthetically prepared turbid water samples have shown that calcium alginate can act as a potential coagulant. The coagulation efficiency was highly dependent on the initial turbidity and calcium concentration. At high initial turbidity, the coagulant worked well, and the targeted final turbidity was achieved at most doses of calcium and alginate. It is stated that the performance is weaker at low turbidity. The authors noted that the use of higher viscosity alginate and prolonged rapid mixing may improve the performance for low turbidity waters [135].

10. Conclusions

Algae are considered a major source of alginate. Since their alginate content and properties are varying, first, the amount to be used should be decided. According to this decision, algae species and the time for growing and harvesting of them must be taken into attention. After that, depending on the area of use, the extraction method should be determined in order to obtain the highest yield of alginate from algal biomass. Now, it is ready to be utilized in different types of sectors. For example, immobilized microalgae networks are open to novel applications. Environmental monitoring and algae-based biosensors comprise one of the promising topics for future developments. Rather than classical bead or thin-film fabrication methods, novel biofabrication techniques can be adapted for algae immobilization, which can help to design customized geometries. Also, as a result of the ability to combine with two different cations to form gel, alginate-contained products show significant elasticity. Unfortunately, algal alginate may contain some impurities like heavy metals, polyphenols, proteins, and endotoxins. In the food industry, low levels of them can be acceptable. But before they are used in cosmetic and pharmaceutic industries, they have to be removed using some purification methods. Alginate NPs have properties such as being biocompatible, nontoxic, and biodegradable. They are safe and preparation of the alginate NPs is easy and so this makes them a potential carrier for drug delivery systems. They can be applied to various drug-delivery systems. Alginate NPs are FDA approved as a food additive and has great mucoadhesive properties, which can make them a potential candidate for drug delivery through the oral route. In agriculture, chitosan/alginate NPs are used mostly for targeted and systemic delivery of agrochemicals, and it has a great potential for prolonged availability and low load of the molecules. Agricultural technology and increase of the fertilizers and pesticides unfortunately made a negative contribution to environment. However, NPs, especially "green NPs," made agriculture more sustainable by using lower doses and slower release of the molecules. Increased awareness of the environmental problems comes with an unavoidable sustainability in all fields, and green NPs are good for environment because their application in agriculture is safe, and also their productions are considered sustainable. However, there are certain limitations to the industrial application of alginate. The most important of these limitations is the exponentially increasing cost with growing scale. For example, coagulants currently used for wastewater treatment are relatively cheaper than algal alginate. However, traditional coagulation processes may require extra costly processes such as pH adjustment or alkalinity addition. Today, in studies about algal alginate, it is possible to increase the efficiency of the system and reduce the cost of coagulation with alginate by using their better and more suitable quality versions.

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